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# Galantamine-Memantine Combination for Cognitive Impairments Due to Electroconvulsive Therapy, Traumatic Brain Injury, and Neurologic and Psychiatric Disorders: Kynurenic Acid and Mismatch Negativity Target Engagement

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## ABSTRACT

Cognitive impairments due to electroconvulsive therapy (ECT), traumatic brain injury (TBI), and neurologic and psychiatric disorders are prevalent. Cholinergic and glutamatergic pathways,  $\alpha$ -7 nicotinic acetylcholine ( $\alpha$ -7nACh) receptor, and *N*-methyl-D-aspartate (NMDA) receptor are potential pathophysiologic mechanisms in all of these conditions. Galantamine not only is an acetylcholinesterase inhibitor but has a dual mode of action as a  $\alpha$ -7nACh receptor modulator as well. Memantine is a noncompetitive NMDA receptor antagonist. Galantamine and memantine are approved by the US Food and Drug Administration (FDA) for the treatment of Alzheimer's disease (AD). Galantamine and memantine have shown efficacy for the treatment of ECT- and TBI-induced cognitive impairments. The kynurenine pathway (KP) metabolites are associated with ECT- and TBI-induced cognitive impairments and several neurologic and psychiatric disorders. Kynurenic acid (KYNA) is an antagonist to the  $\alpha$ -7nACh and NMDA receptors. The galantamine-memantine combination has been shown to modulate several KP metabolites in schizophrenia, thereby improving several cognitive domains. There are no FDA-approved treatments for ECT-induced cognitive impairments or for cognitive impairments in neurologic and psychiatric disorders except AD. This article is timely because the pharmacology of cognition as a panacea for neuropsychiatric diseases was recently published. Hence, randomized controlled trials are warranted with this combination in these diseases, with KYNA and mismatch negativity as novel target engagement. Future positive studies may lead to standard of care, which is likely to significantly improve socio-occupational functioning.

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Cognitive impairments due to electroconvulsive therapy (ECT), traumatic brain injury (TBI), and several neurologic and psychiatric disorders are common. Cholinergic and glutamatergic pathways,  $\alpha$ -7 nicotinic acetylcholine ( $\alpha$ -7nACh) receptor, and *N*-methyl-D-aspartate (NMDA) receptor are potential pathophysiologic mechanisms for cognitive impairments. Galantamine not only is an acetylcholinesterase inhibitor (AChEI) but has a dual mode of action as a  $\alpha$ -7nACh and  $\alpha$ 4 $\beta$ 2 receptor modulator as well.<sup>1</sup> Memantine is a noncompetitive NMDA receptor antagonist,<sup>2</sup> which attenuates the neurotoxic tonic overstimulation of NMDA receptors by glutamate.<sup>3</sup> Memantine modulates Kir6.2 activity (Kir6.2 is a major subunit of the ATP-sensitive K<sup>+</sup> channels and functions in synaptic plasticity); it has been argued that the Kir6.2 channel is a novel therapeutic target to enhance cognition in people with Alzheimer's disease (AD).<sup>4</sup> Galantamine and memantine are approved by the US Food and Drug Administration (FDA) for the treatment of AD. In AD, galantamine 24 mg and memantine 28 mg daily are typically prescribed.<sup>5,6</sup>

The focus of this article is to shed light on cognitive impairments due to ECT, TBI, and neurologic and psychiatric disorders and the potential role of galantamine-memantine combination treatment with kynurenic acid (KYNA) and mismatch negativity (MMN) as target engagement.

## PRECLINICAL EVIDENCE WITH GALANTAMINE-MEMANTINE COMBINATION

Seven preclinical studies<sup>7-13</sup> have shown that the galantamine-memantine combination was effective for cognition; 5 studies<sup>9-13</sup> have shown that the combination was significantly better than either medication alone and also provided synergistic benefits. This evidence may be translated to schizophrenia.<sup>14</sup>

## CLINICAL EVIDENCE WITH GALANTAMINE-MEMANTINE COMBINATION IN ALZHEIMER'S DISEASE AND SCHIZOPHRENIA

In a 53-year-old woman with AD,<sup>15</sup> a combination of donepezil 5 mg and memantine 5 mg for 9 months was ineffective. The patient was switched from donepezil to galantamine (dose unknown). After 4 weeks, irritability and violence gradually decreased and disappeared.<sup>15</sup> Cognition may not have improved because of the inadequate dose and duration of the combination. In a 2-year randomized controlled trial<sup>16</sup> (RCT) with 232 elderly subjects with cognitive impairments, in those with AD prodrome (N = 39), a combination of galantamine and memantine significantly improved cognitive scores compared

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- Galantamine-memantine combination is the standard of care for the treatment of cognitive impairments in Alzheimer's disease.
- Randomized controlled trials are warranted with the galantamine-memantine combination in neuropsychiatric disorders, with kynurenic acid and mismatch negativity as target engagement.
- Clinicians may consider this combination as off-label use, which is likely to significantly improve socio-occupational functioning.

to galantamine alone at 6 months. Cognitive decline occurred after discontinuation of galantamine.<sup>16</sup> In another study,<sup>17</sup> galantamine-memantine combination (N = 53) was significantly better for cognition compared to donepezil-memantine (N = 61) in AD patients. Because the combination was effective in AD, it may be translated to treat cognitive impairments in schizophrenia.<sup>18</sup> Several review articles<sup>19,20</sup> have argued that this combination may be effective for cognitive impairments in schizophrenia. This effectiveness was corroborated in a small open-label study<sup>21</sup> that showed cognitive enhancement in several domains with concurrent improvement in the kynurenine pathway (KP) metabolites. Finally, this combination is the standard of care in AD.

## ELECTROCONVULSIVE THERAPY

ECT is an effective treatment for a variety of psychiatric disorders. ECT is associated with retrograde amnesia (reduced ability to recall recent events) and anterograde amnesia (reduced ability for new learning). ECT-induced cognitive impairments<sup>22</sup> are independent of postictal delirium<sup>23</sup> and are prevalent. In a Swedish register-based study,<sup>24</sup> subjective memory worsening immediately post-ECT was experienced in 26% of 1,212 patients. ECT-induced cognitive impairments are the major factor limiting its use in clinical practice.<sup>25</sup> Bilateral ECT is more effective and faster acting but is associated with more cognitive impairments compared to unilateral ECT.<sup>25</sup> There are no FDA-approved medications for ECT-induced cognitive impairments.

### Pathophysiology of ECT-Induced Cognitive Impairments

The exact mechanisms contributing to ECT-induced cognitive deficits are not well known; however, cholinergic<sup>26</sup> and glutamatergic neurotransmission and NMDA receptor have been implicated<sup>27</sup> among various other factors.

### Clinical Trials With Galantamine for ECT-Induced Cognitive Impairments

In a study by Matthews and colleagues,<sup>28</sup> 9 consecutive ECT patients were given galantamine 4 mg twice daily throughout the course of their ECT treatments followed by a second cohort of 8 consecutive ECT patients who did not receive galantamine. Those who received galantamine

performed significantly better on delayed memory and abstract reasoning items following ECT as measured by the Modified Mini-Mental Status Examination.<sup>29</sup> This measure is an expanded version of the Mini-Mental State Examination (MMSE)<sup>30</sup> that includes additional subtests (delayed recall, similarities, word generation) and has been shown to be effective in screening for cognitive impairments.<sup>31</sup> In an RCT,<sup>32</sup> 39 inpatients diagnosed with major depressive disorder (MDD), bipolar depression, or schizoaffective disorder were randomized to galantamine or placebo. Medications were initiated 24 hours before starting ECT and continued throughout the course of ECT. Galantamine was started at 4 mg twice daily, whereas those assigned to the placebo group received an identical number of inactive tablets twice daily. The dose of galantamine was increased by 4 mg every 3 days to a target dose of 8 mg twice daily. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS),<sup>33</sup> which assesses immediate memory, visuospatial construction, attention, language, and delayed memory, was administered at baseline and 24 to 48 hours after completing a course of ECT. Participants (N = 30; 12 on galantamine, 18 on placebo) had both pre- and posttreatment RBANS ratings. At discharge, those on galantamine scored significantly higher on the delayed memory item compared to the placebo group.<sup>32</sup> Galantamine was safe and well tolerated in both studies.<sup>28,32</sup>

### Clinical Trials With Memantine for ECT-Induced Cognitive Impairments

ECT-induced cognitive impairments may be due to seizure, which leads to irreversible neuron damage by increasing the effect of glutamate on NMDA receptors.<sup>34</sup> On the basis of this hypothesis, memantine has been tried for ECT-induced cognitive impairments. In an RCT,<sup>35</sup> patients with MDD for which ECT was indicated received either memantine 5 mg/day (N = 20) or placebo (N = 20). The patients received memantine or placebo for the whole period of ECT treatment starting the day before ECT and continuing until the fourth session of ECT (total of 8 days because ECT was given on alternate days). The MMSE was used for the assessment of cognition before and at the end of the study. Patients taking memantine scored significantly higher at the end of the ECT sessions compared to those receiving placebo on the MMSE ( $P = .02$ ) and 3-item recall to test recent memory ( $P < .001$ ).<sup>35</sup> In another RCT,<sup>36</sup> adult patients (N = 38) with bipolar disorder, MDD, schizophrenia, or schizoaffective disorder were randomized to memantine (10 mg/day initially and 20 mg/day at the end of the first week) or placebo during the ECT period. The cognitive functions were assessed 24 hours before and after ECT. The mean MMSE score relatively increased in the intervention group and showed a significant improvement with memantine ( $P < .001$ ). The direct digit span score decreased in the control group, whereas no significant change was observed in the intervention group ( $P < .001$ ). Backward memory span test scores decreased in the control group after the ECT sessions, whereas a relative increase was observed

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in the intervention group ( $P=.001$ ).<sup>36</sup> Memantine was well tolerated in both studies.<sup>35,36</sup>

In the study by Abbasinazari and colleagues,<sup>35</sup> it is interesting to note how quickly memantine was effective despite patients receiving only 5 mg starting one day before the first ECT session for a total of 8 days. Memantine was effective despite using a low dose for a short duration. Hence, a higher dose and longer duration would be more effective. Although the 3-item score was significantly better in those taking memantine compared to placebo, even among those taking memantine, the score decreased from 2.9 to 2.6.<sup>35</sup> This finding sheds light on the adequate dose of memantine and indicates that a higher dose may be needed. Perhaps memantine should be started a few days before the first ECT session. Maybe MMSE scores would have returned to baseline if they were measured a few weeks or months after the last ECT session. It is also unclear how long memantine should be continued and how frequently the dose needs to be titrated. The same holds true for galantamine use. Unfortunately, practice guidelines are lacking for the pharmacologic treatment of ECT-induced cognitive impairments.

Galantamine and memantine can be started together.<sup>21</sup> Also, in elderly people with AD, the FDA approved the donepezil-memantine combination (Namzaric), which was found to be safe and well tolerated.

### Clinical Implications

If RCTs find that the galantamine-memantine combination is effective, it may become the standard of care for ECT-induced cognitive impairments. With this combination, bilateral ECT may be administered more often. This treatment modality may be particularly beneficial for those who receive maintenance ECT. Retention deficits resolve only after 6 months; hence, 6-month RCTs are warranted. Also, the galantamine-memantine combination may be administered for 6 months after the last ECT session for faster recovery. This combination treatment may enhance socio-occupational functioning considerably. If cognitive impairments are prevented or treated adequately, there could be less refusal of ECT in real-world practice.

## TRAUMATIC BRAIN INJURY

TBI is common and a major public health problem. TBI-related emergency department (ED) visits, hospitalizations, and deaths have increased over the past decade. In the United States, the total combined rates of TBI-related hospitalizations, ED visits, and deaths increased from 521.0 per 100,000 in 2001 to 823.7 per 100,000 in 2010 (data from the Centers for Disease Control and Prevention).<sup>37</sup> Cognitive impairments due to TBI are common. In a survey,<sup>38</sup> 128 (22%) of 583 patients reported problems with cognition post-TBI.

### Pathophysiology of TBI-Induced Cognitive Impairments

The choline acetyltransferase activity was reduced in the temporal lobe, cingulate, and parietal areas of the neocortex in 16 postmortem human brains following head

injuries compared to 8 controls who died of causes other than central nervous system pathology.<sup>39</sup> In addition to the cholinergic system, the glutamatergic system and NMDA receptors have been implicated in the pathophysiology of TBI.<sup>40,41</sup> Increased level of extracellular glutamate following TBI causes overstimulation of glutamate receptors, leading to neuronal cell death. Glutamate transporter, GLT-1, may be critical in preventing spillover of glutamate between adjacent synapses, thereby regulating intersynaptic glutamatergic and GABAergic transmission.<sup>42</sup> A down-regulation of GLT-1 and GLAST (another glutamate transporter) levels in the ipsilateral and contralateral cerebral cortex is associated with a rise in cerebrospinal fluid glutamate levels, reaching a maximum at 48 hours following the injury.<sup>43</sup> Most patients arrive at the hospital for treatment several hours after the insult; thus, the beneficial use of medications can be very limited.<sup>44</sup> Therefore, early intervention is key. Neuropsychological tests were unable to distinguish cognitive impairments in schizophrenia versus TBI.<sup>45</sup> Unfortunately, there are no FDA-approved medications for TBI-induced cognitive impairments.

### Preclinical Evidence With Galantamine for TBI-Induced Cognitive Impairments

Galantamine enhanced cognitive recovery in adult male rats after TBI.<sup>46</sup> Rats with TBI treated with galantamine showed significant improvements in the Morris water maze, novel object recognition, and context-specific fear memory tasks.<sup>47</sup>

### Clinical Evidence With Galantamine for TBI-Induced Cognitive Impairments

Galantamine 5 mg twice daily was effective for TBI-induced cognitive impairments in 30 patients in an outpatient clinic.<sup>48</sup> In a 28-year-old woman with severe TBI,<sup>49</sup> galantamine 8 mg daily improved cognitive symptoms; she also had psychosis secondary to TBI. Galantamine may be particularly beneficial in people who have both TBI-induced cognitive impairments and psychosis.<sup>50</sup> However, in a 35-year-old man, galantamine 8 mg/day for 1 week did not improve cognition as measured by the MMSE.<sup>51</sup> The authors<sup>50</sup> argued that this lack of improvement could have been due to inadequate dose and duration; also, this patient had history of multiple TBIs. In a 38-year-old man with basal ganglia hemorrhage, galantamine 8 mg/day was started for cognitive impairments.<sup>52</sup> Galantamine was gradually increased to 24 mg/day after 6 weeks. The patient had significant improvement in cognition after 2 months. Despite these improvements, there was no significant improvement on a number of executive functions such as abstract reasoning, and he had low cognitive tolerance for dealing with novel situations and challenges.<sup>52</sup>

### Preclinical Evidence With Memantine for TBI-Induced Cognitive Impairments

In one study, TBI induced in adult rats led to significant neuronal death in the hippocampal CA2 and CA3 regions.<sup>53</sup>

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Treatment of rats with memantine immediately after the injury significantly prevented the neuronal loss in both CA2 and CA3 regions.<sup>53</sup> Vorwerk and colleagues<sup>54</sup> assessed ganglion cell survival and extracellular glutamate levels from 1 to 28 days after optic nerve crush in Long-Evans rats. The optic nerve crush led to a rise in extracellular glutamate, which was blocked by treatment with memantine. Changes in the function of synaptic versus extrasynaptic GluN2B-containing NMDA receptors after mechanical stretch injury in rat cortical neurons were evaluated in another study.<sup>55</sup> Treatment with memantine after TBI prevented injury-induced increases in calcium-permeable AMPA receptor-mediated activity.<sup>55</sup>

Intracranial hemorrhage due to TBI or ruptured cerebral aneurysm is characterized by major neurologic damage and a high mortality rate. Mouse cortical axons degenerated less after exposure to lysed blood in neuronal cultures enriched with both memantine and vitamin D compared to control medium and cultures enriched with only memantine or vitamin D.<sup>56</sup> A combination treatment of 17 $\beta$ -estradiol and memantine was more neuroprotective than either monotherapy in a rat hippocampal slice culture model of TBI.<sup>57</sup> In another study<sup>58</sup> of a rat model of experimental TBI, an intravenous bolus dose of a combination of memantine and 17 $\beta$ -estradiol was administered. The combination was neuroprotective by increasing neuronal survival and decreasing neuronal degeneration in the hippocampus and cortex ipsilateral to injury.<sup>58</sup> This synergistic action may be the result of memantine blocking a deleterious 17 $\beta$ -estradiol-mediated enhancement of NMDA receptors. The melatonin (free radical scavenger)—memantine combination reduced brain injury after TBI in mice compared to either melatonin or memantine<sup>59</sup>; mechanisms were decreased DNA fragmentation, iNOS activity, p38 phosphorylation, ERK-1/2 phosphorylation, and SAPK/JNK-1/2 phosphorylation.

Rat hippocampal slice cultures received 2 stretch injuries 24 hours apart in one study<sup>60</sup>; injury resulted in significant cell death, loss of long-term potentiation (LTP), and astrogliosis compared with uninjured samples. Mice were subjected to repetitive TBI (4 injuries in 4 days) and randomized to memantine or vehicle. Memantine administration 1 hour following each injury significantly reduced the effect of repetitive TBI for all outcome measures. Compared to vehicle-treated mice, memantine-treated mice had reduced tau phosphorylation at acute time points after injury and less glial activation and LTP deficit 1 month after injury.<sup>60</sup> This finding is clinically relevant because repetitive TBI is common in sports concussions and results in significant cognitive impairments.

### Clinical Evidence With Memantine for TBI-Induced Cognitive Impairments

In a 24-week study,<sup>61</sup> 10 patients with severe TBI and 11 patients with mild TBI were treated with memantine or piracetam. Memantine had a positive and stable effect on a broad spectrum of cognitive disturbances, while the effect of piracetam was observed only for some cognitive

functions and was short term.<sup>61</sup> In another study,<sup>62</sup> patients with TBI who received memantine (N = 22) had significantly reduced serum neuron-specific enolase (a marker of neuronal damage) levels by day 7 and marked improvement in their Glasgow Coma Scale scores on day 3 compared to controls (N = 19) who received standard TBI treatment. Memantine may be particularly beneficial in athletes and soldiers in combat who suffer functional impairment and neurodegenerative sequelae after multiple concussions.<sup>63</sup>

### KYNURENINE PATHWAY

KYNA is an antagonist to the  $\alpha$ -7nACh and NMDA receptors. Galantamine-memantine combination may counteract the effects of KYNA, thereby improving cognition.<sup>19-21</sup> ECT administered for 14 days was associated with significant changes in the NMDA receptor complex in rat cortex.<sup>64</sup> This manifest as a reduction in the potency of glycine to inhibit the binding of 5,7-dichloro[3H]KYNA to strychnine-insensitive glycine receptors.<sup>64</sup> Treatment with ECT in 19 patients with MDD was associated with a significant decrease in the plasma concentrations of tryptophan (TRP), kynurenine (KYN), and quinolinic acid (QUIN), whereas concentrations of KYNA did not change.<sup>65</sup> The QUIN/KYNA ratio was found to significantly decrease in ECT-treated patients. There was a significant inverse correlation between symptom severity and KYN concentrations at baseline.<sup>65</sup> In 19 patients with unipolar or bipolar depression, there was a significant increase in KYNA, KYN/TRP, KYNA/KYN, and KYNA/3-hydroxykynurenine ratios post-ECT.<sup>66</sup> KYN and KYN/TRP ratios were significantly negatively associated with total depression scores over time.<sup>66</sup> In another study,<sup>67</sup> before ECT, KYNA concentrations were lower in 50 patients with MDD, bipolar depression, or schizoaffective disorder than in 48 healthy controls. There were no significant changes in those concentrations compared with the baseline concentration during ECT.<sup>67</sup>

In 28 patients with severe TBI, cerebrospinal fluid (CSF) KYN, KYNA, and QUIN were elevated, whereas TRP, anthranilic acid (AA), and 3-hydroxyanthranilic acid (3HAA) remained unchanged.<sup>68</sup> The ratios of QUIN/KYN, QUIN/KYNA, KYNA/KYN, and 3HAA/AA revealed that QUIN concentrations were significantly higher than KYN and KYNA, which is suggestive of increased neurotoxicity.<sup>68</sup> Amplified (indoleamine 2,3-dioxygenase-1 [IDO1] kynurenase [KYNase]) RNA expression was demonstrated in postmortem brains, and enhanced IDO1 protein coincided with overt tissue damage. QUIN concentrations in the CSF were significantly higher in patients with unfavorable outcomes and inversely correlated with Glasgow Outcome Scale scores.<sup>68</sup>

### CEREBROVASCULAR ACCIDENT (STROKE)

Cognitive impairments are common poststroke. Of 105 patients with chronic stroke, 60% had cognitive impairments.<sup>69</sup> In 149 patients with stroke, those with poor

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outcomes had higher mean KYN/TRP ratios than patients with more favorable outcomes.<sup>70</sup> Studies with galantamine and memantine for stroke are scarce; however, these 2 medications have been found to be promising treatments for poststroke cognitive impairments.<sup>71</sup> Hence, the galantamine-memantine combination may be more effective than either medication alone.

## OTHER NEUROLOGIC AND PSYCHIATRIC DISORDERS

The KP is involved in schizophrenia,<sup>72</sup> depression,<sup>73</sup> bipolar disorder,<sup>74</sup> autism spectrum disorder,<sup>75</sup> Down's syndrome,<sup>76</sup> Huntington's disease,<sup>77</sup> HIV/AIDS dementia complex,<sup>78,79</sup> Parkinson's disease,<sup>80</sup> multiple sclerosis,<sup>81</sup> amyotrophic lateral sclerosis,<sup>82</sup> epilepsy,<sup>83</sup> and brain tumors.<sup>84</sup> Thus, the galantamine-memantine combination may be effective for cognitive impairments in these disorders as well. There are no studies conducted with galantamine or memantine in chronic traumatic encephalopathy. This combination may be effective in chronic traumatic encephalopathy, and future studies are warranted.

## NEGATIVE SYMPTOMS

In a study by Oka et al,<sup>85</sup> 36 patients with AD who did not respond to donepezil were switched to galantamine and followed for 24 weeks. Apathy, irritability, aberrant motor symptoms, and executive functioning improved significantly.<sup>85</sup> In the 28-year-old woman with severe TBI mentioned previously who was treated with galantamine, affective flattening and alogia significantly improved.<sup>49</sup> In a 43-year-old man with treatment-refractory schizophrenia, galantamine was associated with a persistent reduction of negative symptoms over the 2-month period of its administration when added to a stable regimen of atypical antipsychotic medications.<sup>86</sup> The patient received galantamine 24 mg for 2 weeks (6 weeks for titration). He had a 50% decrease in the total Scale for the Assessment of Negative Symptoms (SANS); negative symptoms worsened with galantamine discontinuation.<sup>86</sup> Another treatment-refractory male patient with schizophrenia received galantamine 24 mg for 3 months.<sup>87</sup> The patient had global improvement of apathy in the total score on the Marin Apathy Evaluation Scale. In addition, the patient also showed improvements in affective nonresponsivity, anergia, and ability to enjoy sexual interests and activities.<sup>87</sup> In a phase 2 clinical trial,<sup>88</sup> 31 participants with schizophrenia received 3-(2,4-dimethoxybenzylidene) anabaseine (DMXB-A), which is a partial  $\alpha$ -7 nicotinic agonist. Those who received DMXB-A 150 mg twice daily had significant improvement in SANS total score and anhedonia and alogia scores compared to DMXB-A 75 mg twice daily and placebo.<sup>88</sup> In an RCT<sup>89</sup> with galantamine in schizophrenia (N = 86), galantamine significantly improved alogia compared to placebo. This finding is not surprising because galantamine has been shown to improve primary progressive aphasia in frontotemporal dementia.<sup>90</sup> In 45 patients with chronic

poststroke, galantamine administration had a beneficial effect on aphasia.<sup>91</sup> Medications with  $\alpha$ -7 nicotinic action consistently improve alogia, which is an intriguing finding; mechanism of action is unknown.

Memantine treatment reversed anhedonia in stressed rats.<sup>92</sup> Memantine was administered in neonatal rats with early maternal deprivation; social interaction was significantly enhanced in adult rats.<sup>93</sup>

In a 52-year-old man with schizophrenia, memantine 20 mg daily decreased SANS scores from 96 to 70 (avolition-apathy: -8) and anhedonia-asociality (-7), affective flattening (-7), alogia (-1), and attention (-3) in 4 months.<sup>94</sup> In a 72-year-old woman with schizophrenia taking aripiprazole with no obvious psychosis, depression, or extrapyramidal signs, memantine 10 mg/day improved asociality and alogia.<sup>95</sup> Negative symptoms became worse when memantine was stopped and improved with reintroduction of memantine.<sup>95</sup> In an RCT,<sup>96</sup> memantine was also effective for aphasia in 28 patients with chronic poststroke. In another study,<sup>97</sup> participants with deficit schizophrenia (N = 40) showed increased IgA responses to xanthurenic acid, picolinic acid, and quinolinic acid and relatively lowered IgA responses to KYNA and anthranilic acid compared to healthy controls (N = 40) and patients with nondescript schizophrenia (N = 40). In a meta-analysis<sup>98</sup> of 8 RCTs in schizophrenia (N = 448), memantine significantly improved negative symptoms compared to placebo (standardized MD [SMD] = 0.96,  $P = .006$ ).

In a 6-week open-label study<sup>21</sup> of the galantamine-memantine combination in schizophrenia, SANS total score improved from 5 to 0 in 1 participant. This finding is suggestive of improvement of primary negative symptoms, because at baseline, the Brief Psychiatric Rating Scale psychosis, Calgary Depression Scale for Schizophrenia, and the Simpson-Angus Scale scores were 4, 0, and 0, respectively.<sup>21</sup> Negative symptoms are common in the neurologic and psychiatric disorders described previously. Use of galantamine-memantine combination to treat negative symptoms is an additional benefit to patients.

## MISMATCH NEGATIVITY

MMN is the functioning of the auditory sensory memory system indexed by the generation of a well-defined event-related potential. MMN is a biomarker of NMDA<sup>99</sup> and  $\alpha$ -7nACh<sup>100</sup> receptor dysfunction in schizophrenia. MMN is a translatable brain marker toward early intervention for psychosis.<sup>101</sup> In a 6-year follow-up study<sup>102</sup> comparing 48 participants with clinical high risk for psychosis and 47 healthy controls, MMN at baseline was a robust predictor of functional recovery. In another study<sup>103</sup> with 25 participants with schizophrenia, 21 first-degree relatives of participants with schizophrenia, and 29 healthy controls, MMN was a stronger predictor of functional outcome than cognition. Memantine enhanced MMN in 13 healthy subjects,<sup>104</sup> in rodents,<sup>105</sup> and in 41 people with schizophrenia.<sup>106</sup> No studies have been conducted

with galantamine on MMN. However, interactive effects of  $\alpha$ -7nACh and NMDA receptors on MMN were recently published.<sup>107</sup> Therefore, the galantamine-memantine combination may significantly enhance the MMN amplitude more than either medication alone.

## CONCLUSIONS AND FUTURE DIRECTIONS

There is considerable evidence from preclinical and clinical studies for cognitive enhancement with either galantamine or memantine. However, many studies showed an improvement but not recovery. In several studies, various combination treatments were effective.

Galantamine-memantine combination treatment was effective for cognition in AD and showed synergistic benefit in animals. Considering these findings, RCTs are warranted with the galantamine-memantine combination, which may be synergistically better than either medication alone, for ECT-induced cognitive impairments, TBI, and neurologic and psychiatric disorders. This article is timely because the pharmacology of cognition as a panacea for neuropsychiatric diseases was recently published.<sup>108</sup> Positive phase 3 studies may lead to FDA approval for these indications, which is likely to lead to greater clinical utility. This may lead to a significant improvement in patients' functioning in the real world, with KYNA and MMN as target engagement.

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